

No Motivation to Combine the References

The Examiner states that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Posti by substituting the microcrystalline cellulose-excipient taught by Sherwood for the microcrystalline cellulose and silicon dioxide of Posti because of the expectation of achieving excellent disintegration properties and improved compressibility as taught by Sherwood". With regard to the disintegration properties, it is the position of the Applicant that irrespective of which auxiliary agents are used, disintegration properties have not been a problem at any stage of the life-span of clodronate tablets, as clodronate is extremely water-soluble. Accordingly, there is no motivation to combine the teachings of Sherwood to Posti, as the clodronate preparation of Posti does not encounter any problems with disintegration.

With regard to compressibility, Sherwood particularly emphasizes that SMCC has better compressibility when wet granulation is used. The methods disclosed in Sherwood utilize a wet granulation technique, wherein both the active ingredient and SMCC are wet granulated together, or a direct compression technique, wherein both the active ingredient and SMCC are directly compressed without any pretreatment (see Sherwood, page 10, lines 23 to 34). However, neither of these two methods is utilized when the clodronate tablets of the present invention are prepared, nor does Posti utilize the methods of Sherwood. Again,

there is no motivation to combine the teaching of Sherwood and Posti.

In addition, Sherwood mentions that wet granulation is often used in connection with solid dosage forms wherein the amount of active ingredient is high compared to the amount of auxiliary agents. The Applicant points out, however, that the examples of Sherwood describe the preparation of acetaminophen tablets which include only 30% by weight of active agent and 70% SMCC (see Sherwood, page 35, lines 9 to 11). In the present invention, the amount of clodronate is over 60% (64 to 68% in the examples) of the total weight of the composition, and wet granulation is not involved in the preparation of any ingredient of the clodronate tablet of the invention.

Furthermore, clodronate powder is so fine, voluminous, unflowing and sticky that neither direct compression nor wet granulation with any excipient can formulate the clodronate into acceptable tablets. Clodronate powder needs to be first dry granulated and then the granules are lubricated with stearic acid in an ethanol solution in order to form a stearic acid film around the clodronate granules. Then the other ingredients (including SMCC) are added and the mixture is compressed into tablets, corresponding to the method of the present claim 16.

The Examiner should also note that among the long list of therapeutically active agents, which according to Sherwood can be used in conjunction with SMCC, clodronate has not been specifically mentioned, nor does it belong to any of the groups

of active agents mentioned in Sherwood (see page 28, line 31, to page 30, last line, of the Sherwood reference). The Applicant asserts that nothing in Sherwood motivates a person skilled in the art to use SMCC in **clodronate** tablets.

Posti '354, Sherwood, and Remington Do Not Disclose the Unexpected Results of the Present Application

It is the position of the Applicant that the pharmaceutical preparation of the claimed invention surprisingly does not encounter the problem of extensive friability, which is characteristic of clodronate tablets. Support for this can be found in the specification as filed on page 4, beginning on line 10 as well as in Table 2 found on page 11. Additional support with respect to the friability of the tablets is also found in the Declaration that was filed in our previous Office Action response filed March 22, 2002. Neither Posti '354, Sherwood, nor Remington mention this unexpected result of reduced tablet friability. Therefore, the Applicant respectfully requests withdrawal of the 35 U.S.C. §103(a) rejection.

In addition, Remington discloses that colloidal silicon dioxide could be used as a tablet diluent, i.e. as an agent increasing the bulk weight of the material to be tableted. The Applicant is not aware that such purpose of use is disclosed in any other publication in the art. In the enclosed "Handbook of pharmaceutical excipients" 3rd ed., 2000, it is disclosed that silicon dioxide is used as a lubricant in tablets, especially to

improve mass flowability. The same purpose of use is also found in other reference books (for example "Pharmaceutical Dosage Forms, Tablet", Vol. 1, page 162, 1980 and "Pharmaceutical Powder Compaction Technology", page 558, USA 1996, which are also enclosed).

In "Pharmaceutical Powder Compaction Technology," page 558, it is also disclosed that colloidal silica is used as an auxiliary agent when the deleterious effect of magnesium stearate and other lubricants on bonding properties is desired to be limited. In such a situation, the whole mass is first mixed with silicon dioxide and only then with magnesium stearate. Colloidal silica delays the film formation of magnesium stearate around mass particles and consequently limits the weakening effect of magnesium stearate on bonding properties.

When the above-mentioned two advantageous properties of silicon dioxide are known, it can be concluded that the addition of silicon dioxide alone to the mixture should be more advantageous than to add silicon dioxide bound with another auxiliary agent. As silicon dioxide both improves mass flowability and limits the adverse effects of magnesium stearate, it is to be expected that both properties are most effectively established when silicon dioxide may spread and have an effect on the entire mass and all its particles.

Based on the above information, it is not to be expected that when silicon dioxide is bound to another auxiliary agent (microcrystalline cellulose) to form SMCC it could have as an

advantageous effect to the mass properties as when it is spread over the entire mass. Especially when it is taken into account that the amount of active ingredient in the tablets of the invention is extremely high (over 60%), it could not be expected that silicon dioxide bound to a binder (e.g. approx. 13% of the composition) could provide any improvement on the mass properties. On the contrary, based on the above information, a person skilled in the art would expect that when microcrystalline cellulose and silicon dioxide were separately added into the mass, the advantageous effect of them both would be at their highest.

However, the disclosure of the present application (specifically page 4, line 10 onwards and Table 2 on page 11 of the specification, as well as the Declaration filed on March 22, 2002) surprisingly shows that when SMCC is used as a binder, better clodronate tablets are obtained, particularly with regard to friability, compared to the use of MCC alone or to the use of a mixture of MCC and silicon dioxide.

It is to be noted that Sherwood does not even slightly refer to the effect of SMCC on the friability of the exemplified tablets, nor does Sherwood refer to this effect in general. As demonstrated in the declaration filed on March 22, 2002, the results clearly show that that the friability of the tablets made with MCC and SiO_2 is not acceptable under current pharmacopoeial requirements, whereas the tablets made with SMCC had superior results.

The Examiner must present a *prima facie* case of obviousness consisting of references describing each element of the claimed invention and motivation or suggestion to modify or combine the references such that one of ordinary skill in the art had a reasonable expectation of success of making the present composition. Based on the reasons stated above and the results submitted in the declaration filed March 22, 2002, the Applicant asserts that the Examiner has failed to make a *prima facie* case of obviousness. There is no motivation to combine the teachings of Posti '354, Sherwood, and Remington for the reasons stated above, among them being the fact that Sherwood utilizes wet granulation techniques in contrast to the techniques used in Posti '354 and the present invention. Furthermore, combining the teachings of Posti '354, Sherwood, and Remington does not disclose the unobvious result that the clodronate tablets of the present invention do not encounter the problem of extensive friability which is usually a characteristic of clodronate tablets. Based on all of these reasons, the Applicant respectfully requests withdrawal of the 35 U.S.C. §103(a) rejection.

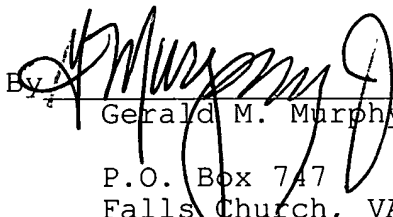
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If the Examiner has any questions regarding the above matters, please contact Applicants' representative, Gerald M. Murphy, Jr., at the telephone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fee required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Enclosures:

- "Handbook of pharmaceutical excipients" 3rd ed., page 143, 2000
- "Pharmaceutical Dosage Forms, Tablet", Vol. 1, page 162, 1980
- "Pharmaceutical Powder Compaction Technology", page 558, 1996